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Dated: December 15, 2011 Signature: /Andrew M. Lawrence/
(Andrew M. Lawrence, Reg. No. 46,130)

Attorney Docket No. 29610/CDT498
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Carl R. Towns et al.

Application No.: 10/578,895

Confirmation No.: 3448

Filed: November 10, 2004 (Int'l. Appl. No.
PCT/GB2004/004754)

Art Unit: 1786

For: Polymers, Their Preparation and Uses

Examiner: B. A. Crouse

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The applicants hereby request that a panel of examiners formally review the legal and factual bases of the claim rejections in the above-referenced application prior to the filing of an appeal brief. It is respectfully submitted that the Office's reasoning for maintaining the claim rejections is based on errors in application of binding legal principles, and should be withdrawn for the reasons concisely described herein.

Submitted herewith is a Notice of Appeal.

Claims 1-42 are pending in this application, but claims 5-42 have been withdrawn. All considered claims 1-4 stand rejected under 35 USC §102(b) as assertedly anticipated by Kobayashi et al., U.S. Patent Publication No. 2003/0168656 ("Kobayashi") as evidenced by Kreuder et al., U.S. Patent No. 6,329,082 ("Kreuder"). All considered claims 1-4 also stand rejected under 35 USC §102(e) as assertedly anticipated by Roberts et al., U.S. Patent Publication No. 2004/0062930 as evidenced by Kreuder.

Specifically, Kreuder was cited to support the Office's assertion that both Kobayashi and Roberts enable "dihalo-substituted dibenzosilole compounds having the substituents as contemplated by applicant." See the office action dated June 15, 2011 at page 7.

The 35 USC § 102 and Rejections Are Traversed

To anticipate a claim, a reference must enable that which it is asserted to anticipate. *See Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed.Cir.2003) (“A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled.”); *Bristol-Myers Squibb v. Ben Venue Laboratories, Inc.*, 58 USPQ2d 1508, 1512 (Fed.Cir.2001) (“To anticipate the reference must also enable one of skill in the art to make and use the claimed invention.”); *PPG Industries, Inc. v. Guardian Industries Corp.*, 37 USPQ2d 1618, 1624 (Fed. Cir.1996) (“To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter.”).

Enablement requires that “the prior art reference must teach one of ordinary skill in the art to make or carry out the claimed invention without undue experimentation.” *Minnesota Mining and Manufacturing Co. v. Chemque, Inc.*, 64 USPQ2d 1270, 1278 (Fed.Cir.2002). The cited art fails to enable the claimed subject matter for at least the reasons described herein.

In first and second/supplemental Rule 132 declarations previously submitted in this application, co-inventor Andrew B. Holmes, Ph.D.¹, explained that neither Kobayashi, Roberts, nor Kreuder enables the synthesis of a polymer comprising a dibenzosilole repeat unit having H or an electron withdrawing group at the 3- and 6- positions as recited by formula (I) in all considered claims 1-4 (“wherein each R is the same or different and represents H or an electron withdrawing group”):



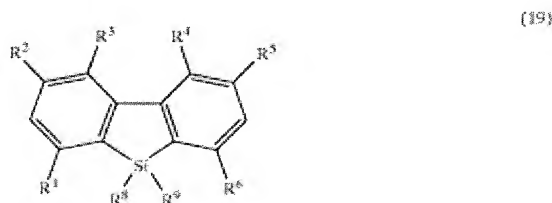
Formula (I)

Reconsideration and withdrawal of the claim rejections are therefore respectfully requested in view of the previously submitted first and second/supplemental Rule 132 declarations and the following comments.

¹ Copies of the “first” Rule 132 declaration submitted with the response dated April 8, 2011 and the “second/supplemental” Rule 132 declaration submitted with the response dated September 15, 2011 are attached hereto as Attachment A and Attachment B, respectively.

Since the advisory action dated October 14, 2011 focused on the claim rejections over Kobayashi as evidenced by Kreuder, these claim rejections are addressed in more detail below. With respect to the claim rejections over Roberts as evidenced by Kreuder, the applicants again request consideration of the declaration evidence previously provided in this application and attached hereto (to the extent such claim rejections are in fact being maintained).

Kobayashi discloses halogenation of a dibenzosilole derivative having formula (19):



either (i) by reaction of the dibenzosilole derivative having formula (19) with the halogenating reagents listed in paragraph [133] or (ii) by reaction of the dibenzosilole derivative having formula (19) with a base selected from the list in paragraph [135] followed by a halogenating agent selected from paragraph [133]. See Kobayashi at paragraphs [0129]-[0135].

The applicants respectfully submit that, like N-bromosuccinimide, all of the other halogenating agents described in paragraph [133] of Kobayashi will generate electrophilic halogenating species. When such electrophilic halogenating species are reacted with a dibenzosilole monomer having H or an electron withdrawing substituent at the 3- and 6-positions (in accordance with the polymer recited in all considered claims), the reaction will firstly be unselective (with respect to the position in which they react with the dibenzosilole derivative having formula (19)), and secondly this lack of selectivity will lead to halodesilylation as explained in the previous Rule 132 declarations (see paragraphs 12-14 of Attachment A and paragraph 5 of Attachment B). Consequently, and consistent with the explanation provided in the previously submitted Rule 132 declarations, the procedure described by Kobayashi is only enabling for dibenzosilole derivatives having formula (19) in which substituents R² and R⁵ are methoxy groups (-OCH₃) and R¹, R³, R⁴, R⁶ are H (i.e., the only 'worked' example in Kobayashi) and possibly in other examples according to formula (19) in which R² and R⁵ are electron-donating substituents, and R¹ = R³ = R⁴ = R⁶ = H. Polymers prepared from such molecules are in stark contrast to the claimed polymers comprising the repeat unit of formula (I) in which H or an electron withdrawing substituent is present at the 3- and 6- positions. Thus, the procedure

disclosed in Kobayashi is not enabling for the preparation of polymers as recited in all considered claims 1-4.

When a base as described in paragraph [135] of Kobayashi is reacted with the dibenzosilole derivative having formula (19), the base is required to selectively remove the hydrogen atoms at the 2- and 7- positions of the dibenzosilole derivative having formula (19) so that the deprotonated product can react with an electrophilic halogenating species generated from a selection of the halogenating agents listed in paragraph [133] of Kobayashi so as to introduce the required halogen atoms at the 2- and 7- positions. When any of substituents R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 is a H atom, however, the reaction of the dibenzosilole derivative having formula (19) with base will be unselective (if indeed it can occur at all) leading eventually to the indiscriminate introduction of halogen atoms at various positions in the molecule and not at the required 2- and 7-positions. Thus, the applicants again respectfully submit that Kobayashi is therefore not enabling for the preparation of polymers comprising the repeat unit of formula (I) in which H or an electron withdrawing substituent is present at the 3- and 6- positions as recited in all considered claims 1-4.

Kreuder merely teaches the well known Sandmeyer reaction, a 19th century process for diazotization of an amino group with nitrous acid (i.e., a reaction with the combination of HCl and NaNO_2 to form a diazonium salt, followed by introduction of bromine (halogen) at the site of the original amino-substituent by reaction with Cu(I)Br). Kreuder does not teach the synthesis of 2,7-diaminodibenzosilole and is therefore also not enabling for the preparation of polymers comprising the claimed repeat unit of formula (I) in which H or an electron withdrawing substituent is present at the 3- and 6- positions as recited in all considered claims 1-4.

CONCLUSION

Reconsideration and withdrawal of all outstanding claim rejections and allowance of all considered claims 1-4 are therefore respectfully requested.

Dated: December 15, 2011

Respectfully submitted,

By /Andrew M. Lawrence/
Andrew M. Lawrence
Registration No. 46,130
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive
6300 Willis Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicants

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Carl Towns et al.)	For: Polymers, Their Preparation
)	and Uses
Serial No. 10/578,895)	
)	Group Art Unit: 1786
Filed: November 10, 2004 (Int'l.)	
Appl. No. PCT/GB2004/004754))	Examiner: Brett Alan Crouse
)	
)	Confirmation No. 3448

DECLARATION UNDER 37 C.F.R. § 1.132 OF ANDREW B. HOLMES, Ph.D.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Andrew B. Holmes, Ph.D., hereby declare as follows:

1. I am a co-inventor of the subject matter claimed in the above-identified patent application (hereafter, "the patent application"). I am familiar with the contents of the patent application.

2. I am a Laureate Professor of Chemistry at the University of Melbourne. I am also an Emeritus Professor at Imperial College London and a Commonwealth Scientific and Industrial Research Organisation (CSIRO) Fellow.

3. I earned B.Sc. and M.Sc. degrees from the University of Melbourne. I was awarded a Ph.D. in 1971 from University College London where my research related to heteroannulenes. After a postdoctoral appointment at E.T.H.-Zurich where I worked on the final stages of the synthesis of vitamin B12, I was appointed to an assistant lectureship at University of Cambridge in 1972. I was awarded tenure and appointed to a lectureship at University of Cambridge in 1977. I became Director of

ATTACHMENT A

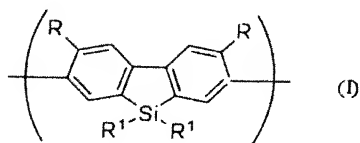
the Melville Laboratory for Polymer Synthesis at University of Cambridge in 1994 and was promoted to a personal Readership in 1995 and to a personal Professorship in 1998. In September 2004, I was appointed Professor of Organic and Polymer Chemistry at Imperial College London, and in October 2004, I was also appointed Australian Research Council (ARC) Federation Fellow and inaugural Victorian Endowment for Science Knowledge Innovation (VESKI) Fellow at the Bio21 Molecular Science and Biotechnology Institute of the University of Melbourne and at the Commonwealth Scientific and Industrial Research Organisation (CSIRO) Division of Materials Science and Engineering. I was elected a Fellow of the Royal Society in 2000, a Fellow of the Australian Academy of Science and a Fellow of the Australian Academy of Technological Sciences and Engineering in 2006.

4. I was Chairman of the Editorial Board of Chemical Communications (2000-2003), have served as a Principal Editor of the Journal of Materials Research (1994-2000) and as a member of the Board of Editors of Organic Syntheses, Inc. (1997-2001), and am currently Associate Editor of Organic Letters (2005-).

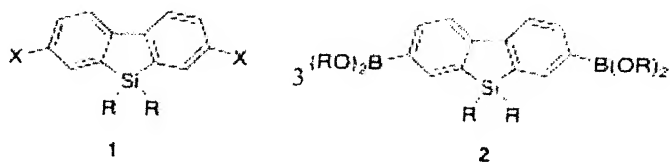
5. My research interests span a range of natural and non-natural synthetic targets. In the natural products area, I have concentrated on biologically active piperidine and indolizidine alkaloids, marine cyclic ethers, and medium ring unsaturated lactams, and the potential application of these materials to alkaloid synthesis and novel peptidomimetics. A recent interest has been the use of phosphoinositides to probe downstream intracellular signaling processes, where the use of phosphatidyl inositol polyphosphate affinity matrices has revealed many new proteins involved in intracellular signaling pathways. My interest in conjugated polymers resulted from an interdisciplinary collaboration with the Cavendish Laboratory at University of Cambridge, which led to the discovery of the first polymeric light emitting diodes and the subsequent interest in organic and polymeric materials for optoelectronic applications.

6. I make this Declaration to provide observations and scientific opinion about the synthetic methods disclosed in U.S. Patent Publication No. 2003/0168656 to Kobayashi et al. (hereafter, "Kobayashi") and U.S. Patent Publication No. 2004/0062930 to Roberts et al. (hereafter, "Roberts").

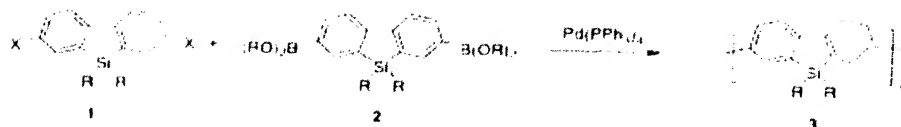
7. I have reviewed Kobayashi and Roberts, and it is my scientific opinion that neither document enables the synthesis of a polymer comprising a dibenzosilole repeat unit, said dibenzosilole repeat unit including a hydrogen or an electron withdrawing group at the 3- and 6- positions, as recited by formula (I; R = H or electron withdrawing group) of claim 1 in the patent application (illustrated below):



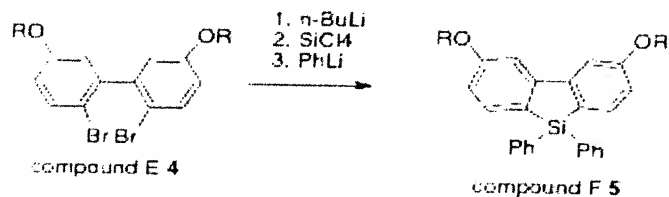
8. Kobayashi generally refers to the synthesis of polydibenzosiloles. One skilled in the art of the controlled synthesis of poly(arylene) conjugated polymers would look to modern methods of organometallic cross coupling for the linkage of aromatic rings to construct a conjugated polymer. The most common method available is the Suzuki polycondensation between a dihalo-substituted aromatic monomer (1) and an aryl bisboronate ester (2). Other methods involve the Yamamoto homopolymerization of a dibromo-substituted aromatic derivative and the Stille cross coupling of an aryl distannane derivative with a dibromo-substituted aromatic species. In all three methods the dihalo-substituted aromatic monomer (1), which can in turn also serve as the precursor of a bisboronate ester or distannane, is required. Therefore, an enabling approach to polydibenzosilole synthesis necessarily includes the capacity to prepare molecules such as (1) and (2), shown below, as suitable components:



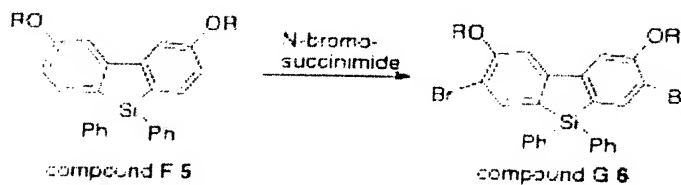
9. To make a polydibenzosilole (3), the corresponding Suzuki reaction would be carried out as shown below:



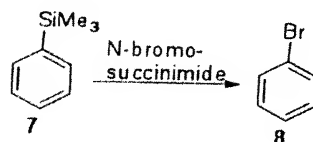
10. The synthesis of dibenzosilole precursors typically requires a transmetalation of a suitable dihalo- precursor, followed by coupling with either SiCl₄ and by displacement of the remaining chlorine atoms with PhLi (as disclosed by Kobayashi), or coupling with a dialkyldihalosilane reagent. Such a reaction is illustrated in Kobayashi (pp. 39-40, Synthetic Example 9) for the conversion of compound E (4) into compound F (5) and a general illustration of this synthesis reaction is shown below:



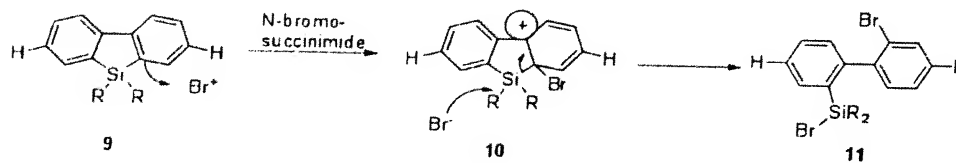
11. The only worked examples reported in Kobayashi for converting compound F (5) into a dihalo-substituted dibenzosilole molecule include the subsequent halogenation of compound F (5) to produce compounds G (6) and H (pp.40-41, Synthetic Example 10) as illustrated by the general synthesis reaction below.



12. The approach illustrated in Kobayashi would fail in the absence of highly electron donating alkoxy (RO-) substituents owing to the very strong electron releasing effect of the bridging Si substituent which in the absence of any competing strong electron donating substituent would lead to halo-desilylation (ipso substitution by electrophilic halogen reagent). The process of halo-desilylation (ipso substitution) is well known to organic chemists skilled in the art as illustrated for the example of the conversion of (7) into (8).



13. Therefore, any attempt to halogenate an unsubstituted dibenzosilole (or one containing any substituent that was less electron donating than RO-) would result in halo-desilylation as illustrated below for the conversion of (9) via (10) into (11).



14. Thus, Kobayashi requires highly electron donating substituents (alkoxy substituents) at the 3- and 6-positions to enable leaving groups to be provided at the adjacent 2- and 7- positions. Consequently, Kobayashi is not enabling for a polymer comprising a dibenzosilole repeat unit having H or an electron withdrawing substituent at the 3- and 6- positions, as recited by formula (I) of claim 1 in the patent application.

15. Roberts only enables preparation of carbon bridged biphenyl derivatives such as fluorenone and dihydrophenanthrene derivatives.

16. For example, Reaction Schemes VIII (p. 31) and X (p. 33) of Roberts teach acid promoted ring closures of biphenyl derivatives to fluorenone derivatives by a process involving intramolecular electrophilic attack of an acyl cation on the adjacent benzene ring (i.e., an intramolecular Friedel Crafts acylation process). Such a reaction is generally illustrated below:



17. Similarly, Reaction Schemes IX (p.32), XI (p.34), and XII (p.35) of Roberts teach preparation of carbon bridged materials in which the atoms forming the carbon bridge are already pre-attached to the aromatic ring. Such a reaction is generally illustrated below:



18. Thus, Roberts only teaches preparation of carbon bridged materials and provides no teachings regarding the synthesis of a polymer comprising a dibenzosilole repeat unit, much less a polymer comprising a dibenzosilole repeat unit having H or an electron withdrawing substituent at the 3- and 6- positions, as recited by formula (I) of claim 1 in the patent application. There is no disclosure in Roberts regarding how Si atoms are introduced into the dibenzosiloles shown as compounds XXXIV and LIV. Consequently, Roberts is not enabling for a polymer comprising a

dibenzosilole repeat unit having H or an electron withdrawing substituent at the 3- and 6- positions, as recited by formula (I) of claim 1 in the patent application.

19. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the above-referenced patent application and any patent issued therefrom.

Date: April 8th, 2011

By

Andrew B. Holmes

Andrew B. Holmes, Ph. D.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Carl Towns et al.)	For: Polymers, Their Preparation
)	and Uses
Serial No. 10/578,895)	
)	Group Art Unit: 1786
Filed: November 10, 2004 (Int'l.)	
Appl. No. PCT/GB2004/004754))	Examiner: Brett Alan Crouse
)	
)	Confirmation No. 3448

DECLARATION UNDER 37 C.F.R. § 1.132 OF ANDREW B. HOLMES, Ph.D.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Andrew B. Holmes, Ph.D., hereby declare as follows:

1. As mentioned in the Declaration under 37 CFR § 1.132 of Andrew B. Holmes, Ph.D. filed April 8, 2011 (hereafter, "the previous Rule 132 Declaration"), I am a co-inventor of the subject matter claimed in the above-identified patent application (hereafter, "the patent application"). I am familiar with the patent application, the June 15, 2011 final action (hereafter, "the final action"), and the documents cited therein.

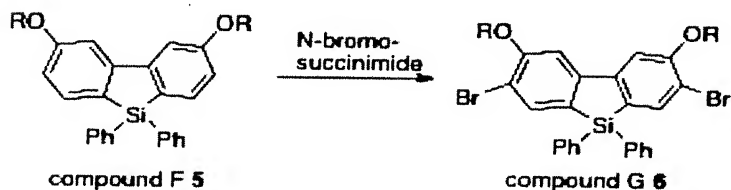
2. At p. 6, section 6 of the final action, the Examiner explained/asserted that:

Kreuder has been added to the rejection over Kobayashi to provide a showing that the public was in possession of the method of making dihalo-substituted dibenzosilole compounds having the substituents as contemplated by applicant. The reference also teaches that the method taught by Kobayashi would successfully result in the production of dihalo-substituted dibenzosilole compounds having the substituents as contemplated by applicant as taught by Kobayashi. Thus, Kobayashi provides an enabling disclosure to one of ordinary skill in the art.

ATTACHMENT B

3. As stated at p. 4, paragraph 11 of the previous Rule 132 Declaration:

The only worked examples reported in Kobayashi for converting compound F (5) into a dihalo-substituted dibenzosilole molecule include the subsequent halogenation of compound F (5) to produce compounds G (6) and H (pp.40-41, Synthetic Example 10) as illustrated by the general synthesis reaction below.

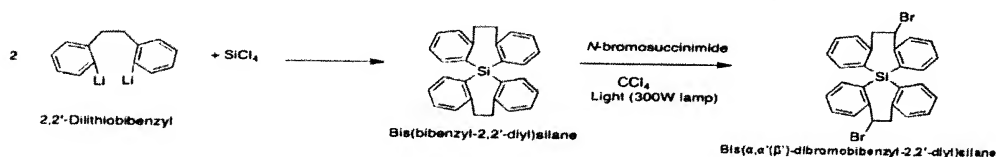


4. Thus, Kobayashi teaches the **aromatic electrophilic bromination** (i.e., substitution of Br^+ for H^+ on the aromatic ring) of an electron rich alkoxy-substituted dibenzosilole using N-bromosuccinimide as illustrated in paragraph 3 (above) and in paragraph 11 of the previous Rule 132 Declaration. The use of N-bromosuccinimide as a mild source of Br_2 (molecular bromine) in aromatic electrophilic brominations is well understood. *See, for example, March, Advanced Organic Chemistry: Reactions, Mechanisms and Structure, 4th ed., John Wiley & Sons, New York, p. 532 (1992), which illustrates the bromination of a phenol using a reagent such as N-bromosuccinimide.*¹

5. As detailed in paragraphs 12-14 of the previous Rule 132 Declaration, the electrophilic bromination reaction allegedly taught by Kobayashi is not enabling for a polymer comprising a dibenzosilole repeat unit having H or an electron withdrawing substituent at the 3- and 6- positions, as recited by formula (I) of claim 1 in the patent application because **halo-desilylation** occurs in the absence of any competing strong electron donating substituent. Thus, Kobayashi does not teach “the production of dihalo-substituted dibenzosilole compounds having the substituents as contemplated by applicant” as asserted by the Examiner. *See final action at pp. 6-7.*

¹ Copy attached as Attachment A.

6. With respect to U.S. Patent No. 6,329,082 to Kreuder et al. ("Kreuder"), the Examiner referenced Example 7 in asserting that Kreuder evidences that Kobayashi has an enabled disclosure. See p. 4 of the final action. In Examples 6 and 7, 2,2'-dilithiobibenzyl is prepared by transmetallation of the corresponding 2,2'-dibromobibenzyl with n-butyl-lithium. Reaction of 2,2'-dilithiobibenzyl with silicon tetrachloride then affords bis(bibenzyl-2,2'-diyl)silane.² Bis(bibenzyl-2,2'-diyl)silane is then reacted with N-bromosuccinimide in carbon tetrachloride in the presence of a light source to obtain bis(α,α' (β')-dibromobibenzyl-2,2'-diyl)silane. The reactions are shown below:



7. The above reaction scheme demonstrates that Kreuder teaches **benzylic side chain halogenations** (i.e., introduction of a halogen reagent to replace a hydrogen atom on a carbon attached to an aromatic ring). Further, the reaction conditions of N-bromosuccinimide in carbon tetrachloride in the presence of a light source corroborate that Kreuder teaches benzylic side chain halogenation. See, for example, March, pp. 694, 695 (1992).³

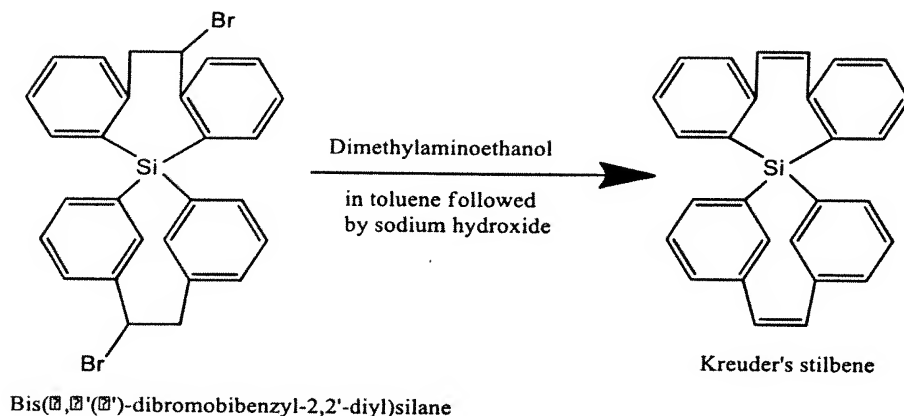
8. In this regard, March teaches that benzylic side chain halogenation is a species of "allylic halogenation." For example, March teaches that "NBS is also a highly regioselective brominating agent at other positions including positions α to a carbonyl group, to a $\text{C}\equiv\text{C}$ triple bond, and to an aromatic ring (benzylic position)." *Id.* at p. 695, lines 17-19. Specific reaction conditions are used in allylic halogenations, for example, "[a] non polar solvent is used, most often CCl_4 ." *Id.* at p. 695, lines 1-2. Further, "[w]ith any reagent [such as N-bromosuccinimide] an initiator is needed; this is usually a peroxide or, less often, uv light." *Id.* at p. 695,

² The structure illustrated at p. 4, section 4 of the final action as corresponding to bis(bibenzyl-2,2'-diyl)silane is incorrect. The correct structure is the middle structure in the scheme illustrated in paragraph 6, above.

³ Copy attached as Attachment A.

lines 4-5. Based on my expertise and experience, a 300W incandescent tungsten lamp as used in Kreuder is also a suitable initiator. Consistent with the foregoing, when discussing promoting aromatic electrophilic substitution, March teaches that “[s]ince side-chain halogenation is catalyzed by light, the reactions should be run in the absence of light wherever possible.” *Id.* at p. 532, lines 11-13. Finally, March discloses that “the mechanism of allylic bromination is of the free radical type....” *Id.* at p. 695, line 21.

9. In Kreuder Example 7, a combination of bis(bibenzyl-2,2'-diyl)silane and “N-bromosuccinimide in 100 ml of **tetrachloromethane** were heated to boiling **under irradiation** with a 300 W incandescent tungsten lamp.” One of ordinary skill in the art would recognize that these reaction conditions lead to benzylic halogenation as the reactive species is a bromine free radical (not molecular bromine) and thus to the right hand compound in the scheme illustrated in paragraph 6 where the bromine atoms are attached to benzylic carbon atoms in the bridging position and not to the aromatic ring. The bromine atoms must be on the bridging positions as the next stage described by Kreuder is a dehydrohalogenation reaction with diethylaminomethanol and then sodium hydroxide to afford the claimed stilbene (see below).



Thus, like Kobayashi, the combination of Kobayashi and Kreuder also does not teach “the method of making dihalo-substituted dibenzosilole compounds having the substituents as contemplated by applicant” as asserted by the Examiner. *See* final action at p. 7.

10. At p. 7 of the final action, the Examiner explained/asserted that:

Kreuder has been added to the rejection over Roberts to provide a showing that the public was in possession of the method of making dihalo-substituted dibenzosilole compounds having the substituents as contemplated by applicant.

11. As stated at pp.6-7, paragraph 18 of the previous Rule 132 Declaration:

...Roberts only teaches preparation of carbon bridged materials and provides no teachings regarding the synthesis of a polymer comprising a dibenzosilole repeat unit, much less a polymer comprising a dibenzosilole repeat unit having H or an electron withdrawing substituent at the 3- and 6- positions, as recited by formula (I) of claim 1 in the patent application. There is no disclosure in Roberts regarding how Si atoms are introduced into the dibenzosiloles shown as compounds XXXIV and LIV. Consequently, Roberts is not enabling for a polymer comprising a dibenzosilole repeat unit having H or an electron withdrawing substituent at the 3- and 6- positions, as recited by formula (I) of claim 1 in the patent application.

12. Kreuder does not remedy any of the previously noted deficiencies in Roberts. Thus, the combination of Roberts and Kreuder does not teach "the method of making dihalo-substituted dibenzosilole compounds having the substituents as contemplated by applicant" as asserted by the Examiner. *See* final action at p. 7.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the above-referenced patent application and any patent issued therefrom.

Date: September 14th, 2011

By

Andrew B. Holmes
Andrew B. Holmes, Ph.D.

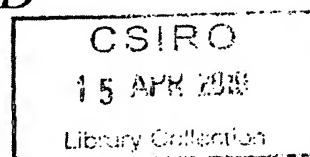
ORGANIC CHEMISTRY

REACTIONS,
MECHANISMS, AND
STRUCTURE

FOURTH EDITION

Jerry March

Professor of Chemistry
Adelphi University



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ATTACHMENT A

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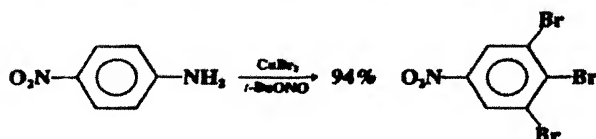
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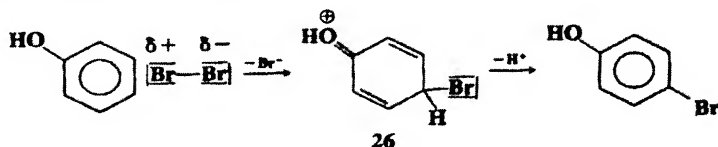
10 9

to the OH_2^+ group, which should be meta-directing because of its positive charge. Bromination and the Sandmeyer reaction (4-25) can be carried out in one laboratory step by treatment of an aromatic primary amine with CuBr_2 and *t*-butyl nitrite, e.g.,¹⁸²



Other reagents have been used, among them HOCl ,¹⁸³ HOBr , and *N*-chloro and *N*-bromo amides (especially *N*-bromosuccinimide and tetraalkylammonium polyhalides¹⁸⁴). In all but the last of these cases the reaction is catalyzed by the addition of acids. Dibromoisocyanuric acid in H_2SO_4 is a very good brominating agent¹⁸⁵ for substrates with strongly deactivating substituents.¹⁸⁶ Two particularly powerful reagents consist of (1) S_2Cl_2 and AlCl_3 in sulfuryl chloride (SO_2Cl_2) (the *BMC reagent*)¹⁸⁷ and (2) dichlorine oxide Cl_2O and a strong acid such as sulfuric.¹⁸⁸ If the substrate contains alkyl groups, side-chain halogenation (4-1) is possible with most of the reagents mentioned, including chlorine and bromine. Since side-chain halogenation is catalyzed by light, the reactions should be run in the absence of light wherever possible.

For reactions in the absence of a catalyst, the attacking entity is simply Br_2 or Cl_2 that has been polarized by the ring.¹⁸⁹



Evidence for molecular chlorine or bromine as the attacking species in these cases is that acids, bases, and other ions, especially chloride ion, accelerate the rate about equally, though if chlorine dissociated into Cl^+ and Cl^- , the addition of chloride should decrease the rate and the addition of acids should increase it. The conjugate base of 26 (4-bromo-2,5-cyclohexadienone) has been detected spectrally in the aqueous bromination of phenol.¹⁹⁰

When a Lewis-acid catalyst is used with chlorine or bromine, the attacking entity may be Cl^+ or Br^+ , formed by $\text{FeCl}_3 + \text{Br}_2 \rightarrow \text{FeCl}_3\text{Br}^+ + \text{Br}^-$, or it may be Cl_2 or Br_2 , polarized by the catalyst. With other reagents, the attacking entity in brominations may be Br^+ or a species such as H_2OBr^+ (the conjugate acid of HOBr), in which H_2O is a carrier of Br^+ .¹⁹¹

¹⁸²Doyle; Van Lente; Mowat; Fobare *J. Org. Chem.* 1980, 45, 2570.

¹⁸³For the use of calcium hypochlorite, see Nwaukwa; Keehn *Synth. Commun.* 1989, 19, 799.

¹⁸⁴See Kajigaeshi; Moriawaki; Tanaka; Fujisaki; Kakinami; Okamoto *J. Chem. Soc., Perkin Trans. 1* 1990, 897, and other papers in this series.

¹⁸⁵Nitrobenzene is pentabrominated in 1 min with this reagent in 15% oleum at room temperature.

¹⁸⁶Gottardi *Monatsh. Chem.* 1968, 99, 815, 1969, 100, 42.

¹⁸⁷Ballester; Molinet; Castañer *J. Am. Chem. Soc.* 1960, 82, 4254; Andrews; Glidewell; Walton *J. Chem. Res. (S)* 1978, 294.

¹⁸⁸Marsh; Farnham; Sam; Smart *J. Am. Chem. Soc.* 1962, 104, 4680.

¹⁸⁹For reviews of the mechanism of halogenation, see de la Mare, Ref. 171; de la Mare; Swedlund, in Patai *The Chemistry of the Carbon-Halogen Bond*, pt. 1; Wiley: New York, 1973; pp. 490-536; Taylor, in Bamford; Tipper, Ref. 1, pp. 83-139; Berliner *J. Chem. Educ.* 1966, 43, 124-133. See also Schubert; Dial *J. Am. Chem. Soc.* 1975, 97, 1877; Keefer; Andrews *J. Am. Chem. Soc.* 1977, 99, 5693; Briggs; de la Mare; Hall *J. Chem. Soc., Perkin Trans. 2*

With HOCl in water the generally AcOCl . All the doubtful that Cl^+ is a significant entity in the reaction demonstrated in the reaction of chlorine attacking entity at ranges (as in 1-35) to give isomer predominates.¹⁹³

FeCl_3 itself, and also Cl_2 . The electrophile might be by a free-radical mechanism.

When chlorination or bromination with ortho-para-directing groups here, which is not complete by the SEI mechanism, e.g. zene.¹⁹⁸

2. Iodine. Iodine is the for active substrates, an oxidizing electrophile.²⁰⁰ Examples of and H_2O_2 .²⁰¹ ICl is a better used have been IF (preparation of dichloriodate (which amines),²⁰⁴ and the combination of reagent for active substrates substrate with I_2 in the presence of $\text{CF}_3\text{SO}_3\text{Ag}$,²⁰⁸ $\text{HgO}-\text{BF}_3$,²⁰⁹ the TiOAc method is regioselective.

The actual attacking species is too unreactive, except for active

¹⁹²Swain; Crist *J. Am. Chem. Soc.* 1953; Paul *J. Am. Chem. Soc.* 1976.

¹⁹³Haberfeld *J. Org. Chem.* 1976.

¹⁹⁴Kovacic; Wu; Stewart *J. Am. Chem. Soc.* 1976.

¹⁹⁵Commandeur; Mathais; Raynier; Wacziarg *J. Org. Chem. USSR* 1988, 24, 211; K.

¹⁹⁶For a review of halogenations with I_2 , see Nonhebel *J. Chem. Soc.* 1963, 1.

¹⁹⁷For a review of this type of reaction, see Mach; Bunnett *J. Am. Chem. Soc.* 1977, pp. 227-276.

¹⁹⁸For reviews of I_2 as an electrophile, see 1977, pp. 227-276. For reviews of aromatic iodination, see 1984, 53, 343-350.

¹⁹⁹Butler *J. Chem. Educ.* 1971, 48, 100.

²⁰⁰For a discussion, see Makhon'ko; Uemura; Onoe; Okano *Bull. Chem. Soc. Jpn.* 1971, 44, 100.

²⁰¹For a review of ICl , see McClellan; Rozen; Zamir *J. Org. Chem.* 1971, 36, 100.

²⁰²See Kajigaeshi; Kakinami; Watanabe *J. Org. Chem.* 1971, 36, 100.

²⁰³Radner *Acta Chem. Scand.* 1969, 23, 5287.

²⁰⁴Baird; Surridge *J. Org. Chem.* 1971, 36, 100.

²⁰⁵Uemura; Onoe; Okano *Bull. Chem. Soc. Jpn.* 1971, 44, 100.

²⁰⁶Kobayashi; Kumadaki; Yoshida *J. Org. Chem.* 1971, 36, 100.

²⁰⁷Koveshnikova *Synthesis* 1980, 486.

²⁰⁸Barluenga; Camos; Gonzalez *J. Org. Chem.* 1971, 36, 100.

TABLE 14.4 Some D values¹⁰⁰

Bond	D	
	kcal/mol	kJ/mol
H-F	136	570
H-Cl	103	432
H-Br	88	366
H-I	71	298
F-F	38	159
Cl-Cl	59	243
Br-Br	46	193
I-I	36	151
CH ₃ -F	108	452
CH ₃ -Cl	85	356
CH ₃ -Br	70	293
CH ₃ -I	57	238

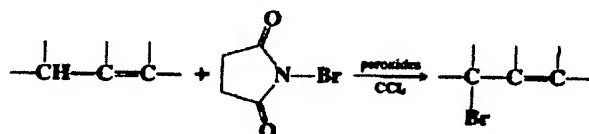
to be $F_2 > Cl_2 > Br_2 > I_2$ is the decreasing strength of the HX bond in the order $HF > HCl > HBr > HI$. The increased reactivity of secondary and tertiary positions is in accord with the decrease in D values for R-H in the order primary > secondary > tertiary (Table 5.3). (Note that for chlorination step 1 is exothermic for practically all substrates other than CH_4 , since most other aliphatic C-H bonds are weaker than those in CH_4 .)

Bromination and chlorination of alkanes and cycloalkanes can also take place by an electrophilic mechanism if the reaction is catalyzed by $AgSbF_6$.¹¹² Direct chlorination at a vinylic position by an electrophilic mechanism has been achieved with benzeneselenenyl chloride $PhSe(O)Cl$ and $AlCl_3$ or $AlBr_3$.¹¹³ However, while some substituted alkenes give high yields of chloro substitution products, others (such as styrene) undergo addition of Cl_2 to the double bond (5-26).¹¹³ Electrophilic fluorination has already been mentioned (p. 690).

OS II, 89, 133, 443, 549; III, 737, 788; IV, 807, 921, 984; V, 145, 221, 328, 504, 635, 825; VI, 271, 404, 715; VII, 491; 65, 68.

4-2 Allylic Halogenation

Halogenation or Halo-de-hydrogenation



This reaction is a special case of 4-1, but is important enough to be treated separately.¹¹⁴ Olefins can be halogenated in the allylic position by a number of reagents, of which N-bromosuccinimide (NBS)¹¹⁵ is by far the most common. When this reagent is used, the

¹¹²Olah; Renner; Schilling; *Mo J. Am. Chem. Soc.* 1973, 95, 7686. See also Olah; Wu; Farooq *J. Org. Chem.* 1969, 34, 1463.

¹¹³Ucciani; Naudet *Bull. Soc. Chim. Fr.* 1968, 44, 110.

REACTION 4-2

reaction is known as *Wohl-CCl₄*. Other N-bromo amide nation has been carried on sulfonamide,¹¹⁶ or *t*-butyl h usually a peroxide or, less o

The reaction is usually q However, when the allylic ra take place, so that mixtures



When a double bond has t secondary position is substit tertiary hydrogen is not clea been performed.¹¹⁸ It is possi the electron-withdrawing nat side of the double bond rath

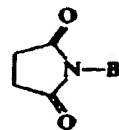
NBS is also a highly regio sitions α to a carbonyl grou position). When both a doub position is α to the triple bon

That the mechanism of all by Dauben and McCoy,¹²¹ w initiators and inhibitors and i is present. Subsequent work i the substrate is the bromine i it is formed, the main propag

Step 1

Step 2

The source of the Br_2 is a step 1:



The function of the NBS is concentration and to use up

¹¹⁶Thellacker; Wessel *Liebigs Ann.*

¹¹⁷Walling; Thaler *J. Am. Chem. Soc.*

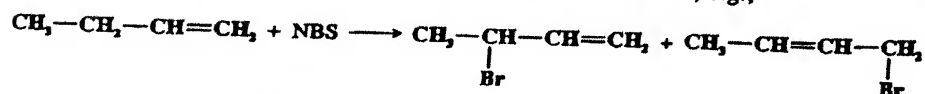
¹¹⁸Dauben; McCoy *J. Org. Chem.*

¹¹⁹Ucciani; Naudet *Bull. Soc. Chim. Fr.*

¹²⁰Pailler *Bull. Soc. Chim. Fr.* 194

reaction is known as *Wohl-Ziegler bromination*. A nonpolar solvent is used, most often CCl_4 . Other N-bromo amides have also been used. To a much lesser extent, allylic chlorination has been carried out, with N-chlorosuccinimide, N-chloro-N-cyclohexylbenzenesulfonamide,¹¹⁶ or *t*-butyl hypochlorite.¹¹⁷ With any reagent an initiator is needed; this is usually a peroxide or, less often, uv light.

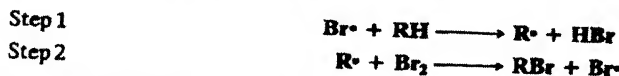
The reaction is usually quite specific at the allylic position and good yields are obtained. However, when the allylic radical intermediate is unsymmetrical, allylic rearrangements can take place, so that mixtures of both possible products are obtained, e.g.,



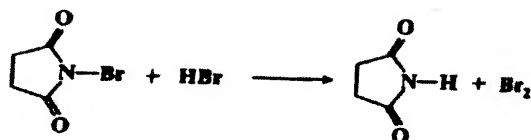
When a double bond has two different allylic positions, e.g., $\text{CH}_3\text{CH}=\text{CHCH}_2\text{CH}_3$, a secondary position is substituted more readily than a primary. The relative reactivity of tertiary hydrogen is not clear, though many substitutions at allylic tertiary positions have been performed.¹¹⁸ It is possible to brominate both sides of the double bond.¹¹⁹ Because of the electron-withdrawing nature of bromine, the second bromine substitutes on the other side of the double bond rather than α to the first bromine.

NBS is also a highly regioselective brominating agent at other positions, including positions α to a carbonyl group, to a $\text{C}\equiv\text{C}$ triple bond, and to an aromatic ring (benzylic position). When both a double and a triple bond are in the same molecule, the preferred position is α to the triple bond.¹²⁰

That the mechanism of allylic bromination is of the free-radical type was demonstrated by Dauben and McCoy,¹²¹ who showed that the reaction is very sensitive to free-radical initiators and inhibitors and indeed does not proceed at all unless at least a trace of initiator is present. Subsequent work indicated that the species that actually abstracts hydrogen from the substrate is the bromine atom. The reaction is initiated by small amounts of Br^\cdot . Once it is formed, the main propagation steps are



The source of the Br_2 is a fast ionic reaction between NBS and the HBr liberated in step 1:



The function of the NBS is therefore to provide a source of Br_2 in a low, steady-state concentration and to use up the HBr liberated in step 1.¹²² The main evidence for this

¹¹⁶Thellacker; Wessel *Liebigs Ann. Chem.* 1967, 703, 34.

¹¹⁷Walling; Thaler *J. Am. Chem. Soc.* 1961, 83, 3877.

¹¹⁸Dauben; McCoy *J. Org. Chem.* 1959, 24, 1577.

¹¹⁹Ucciani; Naudet *Bull. Soc. Chim. Fr.* 1962, 871.

¹²⁰Felber *Bull. Soc. Chim. Fr.* 1963, 537.